REMARKS

Claims 10, 11, 179, 181, 182, and 187-196 are pending in the present application. By this response, claims 10, 11, 181 and 189 have been amended and new claims 197-209 have been added. Accordingly, claims 10, 11, 179, 181, 182, and 187-209 are currently under consideration. No new matter is added by the amendments and new claims, and entry of the amendments is respectfully requested.

With respect to claim amendments and cancellations, Applicants have not dedicated to the public or abandoned any unclaimed subject matter and have not acquiesced to any rejections and/or objections by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Reconsideration of the application is respectfully requested in view of the following remarks. For the Examiner's convenience, Applicants' remarks are presented in the order in which they were raised in the Office Action.

A. Claim Amendments

Claims 10, 11, 181 and 189 are amended to recite that the control animal is a "non-transgenic or transgenic" mouse throughout the claims. Support for the amendment is found at pages 77-78, 94-96 and Figs. 3A-3D, 4A-4D, 8A-8E and 9A-9D of the specification.

New claims 197-208 recite that development of hepatocellular carcinoma could be selected from "selected from the group consisting of growth, proliferation and metastasis of hepatocellular carcinoma." these claim terms were previously suggested as targets for modulation of HCC by the Examiner in the Office Action dated June 14, 2007. Support for the amendment is found at pages 21, 78, 90, 92-93, 95 and throughout the specification.

New claim 209 is directed to a screening method for modulators of dysplasia or neoplasia associated with hepatocellular carcinoma and finds support at page 94 of the specification.

No new matter is added by the amendments and new claims, and entry of the amendments and new claims is respectfully requested.

B. Claim Rejections – 35 USC § 112, first paragraph

Claims 10, 11, 189, and claims 179, 181-182, 187-188, and 190-196 dependent therefrom stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement.

The Examiner argues that the specification, while being enabling for a FGF19 transgenic mouse wherein transgene is expressed under the control of a MLC promoter and wherein said transgenic mouse has a phenotype of developing hepatocellular carcinoma (HCC), allegedly is not enabled for an HCC mouse wherein the FGF19 gene is driven by any promoter. In support, the Examiner cites Roberts (Toxicology Letters 112:49-57 (2000)) for stating that peroxisome proliferator mediated hepatocarcinomas exhibit species differences possibly due to differences in ACO promoter sequences between human and rat promoters. The Examiner concludes that a skilled artisan will have to resort to undue experimentation to identify gene promoters for the ability to induce hepatocarcinogenesis in mice expressing FGF-19. Applicants respectfully traverse.

First, Applicants note that Roberts relates to expression of an intracellular gene acyl CoA oxidase (ACO) in response to a hepatocarcinogen. Roberts discloses a human ACO promoter that is unable to drive PP-mediated gene expression in the presence of PPAR-alpha in contrast to the rat ACO promoter. Roberts provides a hypothesis that the species difference in the response is caused by differences in promoter sequences. (Roberts pp. 54-57.)

In contrast, the claimed invention relates to an "integrated transgene encoding FGF19 operably linked to a promoter, wherein said transgene results in said mouse developing hepatocellular carcinoma." (*See* for example, claim 1.) The specification states that the transgenic mouse expresses FGF19 in muscle and hepatocellular carcinoma is induced in the liver. ("To understand in vitro effects of FGF19, transgenic mice over-expressing FGF19 in skeletal muscle were generated. By 10 months of age, hepatocellular carcinoma (HCC) developed in the FGF19 transgenic mice." Specification, Example 8, page 90, first full paragraph.) The instant invention, for

the first time, shows ectopic expression of an oncogene leading to hepatic cancer. (Specification at p. 90, lines 18-19.) As described in the specification, FGF-19 is expressed in the skeletal muscle (*see* specification at p. 90), secreted in the serum (*see* specification at pp. 91-92, 94) and acts on the liver to induce hepatocellular carcinoma (*see* specification at p. 94).

As recited in claim 1, "integrated transgene encoding FGF19 [is] operably linked to a promoter, wherein said transgene results in said mouse developing hepatocellular carcinoma." The claim requires that the FGF19 is expressed via the promoter in a manner sufficient be secreted and delivered to the liver to induce development of hepatocellular carcinoma.

One of skill in the art would know that in order to practice the claimed method of screening recited in claims 10, 11 and 189 and new claim 209, the transgenic mouse must comprise an "integrated transgene encoding FGF19 operably linked to a promoter" wherein such promoter acts to express FGF19 in a manner that induces hepatocellular carcinoma in the liver. The specification provides ample guidance as to the detection of hepatocellular carcinoma in the transgenic mice. (Specification at p. 94, *inter alia.*)

Second, Applicants submit that in addition to the MCL promoter disclosed in the specification, one of skill in the art would have been aware of numerous promoter systems that would be suitable for expression of a growth hormone transgene as of the priority date of the application. For example,[1]

- Morello et al. (The EMBO J., 5(8):1877-1883 (1986)) discloses transgenic mice carrying a H2K promoter linked to a human growth hormone gene which is expressed in all tissues examined.
- Idzerda et al. (Mol. Cell. Biol. 9(11):5154-5162 (1989) discloses transgenic mice carrying a transferrin gene promoter linked to a human growth hormone gene which is expressed in liver, brain and testis.

- Palmiter et al. (Science 222:809-814 (1983) discloses transgenic mice carrying a metallothionein gene promoter linked to a human growth hormone gene which is expressed in several tissues.

- Bchini et al. (Endocrinology. 128(1):539-46 (1991)) discloses transgenic mice carrying a HMG-CoA gene promoter linked to a human growth hormone gene which is expressed in all tissues and results in circulating hGH.

- Brar et al. (Endocrinology. 125(2):801-809 (1989)) discloses transgenic mice carrying a mouse metallothionein-1 promoter linked to a human GH-releasing hormone (hGRH) gene wherein hGRH expression in the transgenic mice occurs in a cell-specific manner in the hypothalamus as well as in numerous other tissues, many of which have secretory functions.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. (*Genentech Inc. v. NovoNordisk A/S* 108 F.3d 1361, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997)). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991.)

Since (a) one of skill in the art would have been able to choose from several promoter options for generating an "integrated transgene encoding FGF19 operably linked to a promoter," (b) the claims specify that a further selection be made based on the induction of hepatocellular carcinoma, and (c) the Specification provides ample guidance as to the detection of hepatocellular carcinoma in the transgenic mice (Specification at p. 94, *inter alia*), Applicants submit that the claims are enabled for the full scope of a "transgene encoding FGF19 operably linked to a promoter" and narrowing of the claims to the specific MCL promoter used in the examples of the Specification is not warranted. Applicants respectfully request withdrawal of this rejection.

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[1] Copies of the references are submitted herewith for the Examiner's convenience and included in a supplementary information disclosure statement (SIDS).

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to allow this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to ***Deposit Account No. 03-1952*** referencing docket no. **146392001900**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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